Bromfenac ophthalmic solution 0.09% as an adjunctive therapy to topical steroids after cataract surgery in pseudoexfoliation syndrome

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PURPOSE: To study with laser flare photometry the antiinflammatory effect of bromfenac added to a topical steroid versus a topical steroid alone in patients with pseudoexfoliation (PXF) syndrome after cataract surgery.

SETTING: Ophthalmology Unit, Santa Maria Nuova Hospital, Reggio Emilia, Italy.

DESIGN: Randomized clinical trial.

METHODS: Patients with cataract and clinical signs of PXF were randomized to dexamethasone 0.1% and tobramycin 0.3% ophthalmic solution (Group 1) or with the adjunct of bromfenac ophthalmic solution 0.09% (Group 2). All patients were examined on the day of surgery (baseline) and postoperatively at 1, 3, 7, and 30 days. Laser flare photometry was used to quantify anterior chamber inflammation and optical coherence tomography to measure macular thickness.

RESULTS: Sixty-two patients were included. Postoperatively, the mean flare was 31% lower in Group 2 than in Group 1 at 3 days (11.92 ph/msec ± 8.14 [SD] versus 17.13 ± 9.03 ph/msec; $P = .025$) and 43% lower at 7 days (10.77 ± 6.17 ph/msec versus 18.72 ± 12.37 ph/msec; $P = .003$). There were no significant differences in postoperative visual acuity, symptoms, or ocular pain between groups. The mean macular thickness 1 month after surgery was increased in Group 1 but not Group 2; the difference between groups was significant at 4 weeks ($P = .03$). The incidence of intraretinal cysts was higher in Group 1 (n = 4) than in Group 2 (n = 0).

CONCLUSION: The addition of bromfenac to topical steroids after cataract surgery in eyes with PXF was associated with greater reductions in inflammation than steroids alone.

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Pseudoexfoliation syndrome (PXF) represents one of the most common challenges encountered during cataract surgery.[1] The prevalence in the United States is up to 14%[2] and is related to aging and low climatic temperature.[3] Also known as Viking disease, PXF is more common in Northern Europeans. In Sweden, an 87-year-old individual has a 61% chance of having PXF.[4] Pathologic features include deposition of a white fibrillar material in the anterior segment of the eye. This matrix of granular amyloid-like proteins can be found also in other organs.[2]

Postoperative inflammation is higher in PXF cataracts than in routine cataracts.[1,5,6] This is the result of a constitutively damaged blood–aqueous barrier (BAB) that leads to increased leakage of serum proteins into the aqueous humor after surgery (flare or Tyndall effect).[1,7] The fragility of the BAB and intense postoperative inflammation might be responsible for a higher risk for pseudophakic macular edema in PXF eyes.[8–10]

Ophthalmic nonsteroidal antiinflammatory drugs (NSAIDs) are approved for the treatment of inflammation and pain after cataract surgery.[8,11] Bromfenac

sodium sesquihydrate is the most recently introduced agent in this class.[12–17] Although topical NSAIDs control anterior segment inflammation after cataract surgery, there is lack of consensus about whether they should be given on a routine basis in addition to topical steroids.[11,18] Steroids were believed to be more effective than NSAIDs because they inhibit phospholipase, an enzyme higher in the inflammatory cascade than cyclooxygenase (the target of NSAIDs).[19] However, ophthalmic NSAIDs might be more efficient than topical steroids at reestablishing the BAB after surgery.[8,11] Nonsteroidal antiinflammatory drugs have also been shown to prevent formation of postoperative macular edema in some,[11,19,20] but not all,[21] studies.

Difficulties in measuring ocular inflammation limit the ability to evaluate NSAID efficacy after cataract surgery.[11] The current grading system was developed to assess uveitis and is based on subjective examination of the anterior chamber at the slitlamp,[22] which is semiquantitative and has a low reproducibility.[23] Laser flare meters allow precise measurement of inflammatory protein concentrations in the aqueous humor in vivo.[24]

Patients with PXF who have high levels of postoperative ocular inflammation might represent an ideal population in which to assess the efficacy of NSAIDs for reducing postoperative inflammation after phacoemulsification; however, the effects of NSAIDs in eyes with PXF have not been studied to date. This study evaluated the antiinflammatory effects of bromfenac 0.09% when added to a topical steroid versus a steroid alone after cataract surgery in patients with PXF.

PATIENTS AND METHODS

Study Design

This single-center assessor-blinded randomized trial was performed at the Ophthalmology Unit, Istituto di Ricerca e Cura a Carattere Scientifico-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, between November 2013 and October 2014. The study protocol was approved by the local ethics committee, and the trial was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. The study was registered with the U.S. National Institutes of Health Clinical Trials[A] and the European Clinical Trials Register.[B]

Inclusion and Exclusion Criteria

Patients aged 60 years or older were eligible for inclusion if they had cataract and clinical signs of PXF. Cataract was defined as nuclear sclerosis of the crystalline lens graded as 1 or more according to the Lens Opacities Classification System III.[25] Diagnosis of PXF was made at the slitlamp after pupil dilation based on visualization of pathognomonic white deposits in the anterior surface of the lens and the pupillary margin. Other inclusion criteria were no topical, systemic, or inhaled NSAIDs within 1 week of surgery and no topical, inhaled, or systemic corticosteroids within 15 days of surgery.

Patients were excluded if they had known hypersensitivity to any component of the investigational products, procedural medications, salicylates, or other NSAIDs; uncontrolled chronic ocular or systemic disease; a history of ocular inflammation or trauma; previous surgery in the study eye; any form of corneal haze; retinal vascular disease or diabetic retinopathy; alteration of the fovea, such as macular edema or epiretinal membrane; or moderate to severe age-related macular degeneration. Use of corticosteroids, NSAIDs, opioids, narcotics, and tamsulosin during the study was not permitted. Patients who had intraoperative complications such as posterior capsule rupture with vitreous loss and patients who developed postoperative anterior acute uveitis with keratic precipitates were excluded from final data analysis.

Preoperative Glaucoma and Treatment Medication

The number of glaucoma drugs taken was recorded and grouped into 4 classes as follows: α-agonists, ß-blockers, carbonic anhydrase inhibitors, and prostaglandin analogs. Prostaglandin analogs were discontinued the day before surgery and substituted with dorzolamide 2.0% and timolol 0.5% twice daily during the study.

Bromfenac ophthalmic solution 0.09% (Yellox) and dexamethasone 0.1% and tobramycin 0.3% eyedrops (Tobradex) were supplied by the hospital dispensary.

Eligible patients who signed the consent form were randomized (1:1 ratio) using computer-generated randomization codes to dexamethasone and tobramycin alone (Group 1) or dexamethasone and tobramycin plus bromfenac (Group 2).

Surgical Technique

All patients had standard phacoemulsification and intraocular lens (IOL) implantation in the capsular bag. Cataract surgeries were performed by 1 of 2 experienced surgeons (L.F., A.S.), masked to randomization using the Whitestar Signature phacoemulsification system (Abbott Medical Optics Inc.) through a 2.2 mm temporal clear cornea incision. The same ophthalmic viscosurgical device (sodium hyaluronate 1.4% [Healon GV]) and acrylic IOL (AR40e, Abbott Medical Optics, Inc.) were used in all patients. The duration of surgery was recorded.

The day after surgery, all patients started treatment with dexamethasone 0.1% and tobramycin 0.3% eyedrops (4 times

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daily for the first week, twice daily the following week). Patients randomized to bromfenac also received bromfenac ophthalmic solution 0.09% twice daily for 2 weeks. Bromfenac is registered in the European Union as a 0.09% formulation only, and its use is approved for 14 days postoperatively only; no preoperative treatment is allowed.

Outcome Measures

The primary efficacy endpoint was a 30% reduction in flare in Group 2 versus Group 1 from baseline to postoperatively at 3 days; the levels of flare at 7 and 30 days were also measured. Anterior chamber flare was evaluated with a laser flare meter (FM-700, Kowa Co. Ltd.) that uses a diode laser beam to quantify protein concentration in the aqueous humor.[24] Measurements and calibration of the instrument were performed following the manufacturer's recommendations.

Secondary endpoints were the proportion of patients with 20/20 corrected distance visual acuity (CDVA) at 1 week, the proportion of patients with no ocular pain at 3 days, and the proportion of patients with central macular thickness with optical coherence tomography (OCT) more than 300 μm at 4 weeks.

Patient Assessments

All patients were examined on the day of surgery (baseline) and postoperatively at 1 day, 3 days, 7 days (±1 day), and 30 days (±3 days). Clinical examination by slitlamp biomicroscopy and dilated fundus examination, intraocular pressure (IOP) by pneumotonometry, CDVA, and laser flare photometry measurements were performed at each visit. The CDVA was assessed using an electronic Snellen chart, and readings were converted to logMAR values. Optical coherence tomography (OCT) (3D OCT-2000, Topcon Europe Medical B.V.) was used to quantify macular thickness at baseline, 1 week, and 4 weeks. Measurements of CDVA, IOP, laser flare photometry, and OCT were performed by a certified technician unaware of treatment allocation. Ocular discomfort was determined using the patient-reported Ocular Comfort Grading Assessment (OCGA).[14] Patients graded each symptom as none (0), mild (1), moderate (2), or severe (3) at each visit. The presence of intraretinal cysts in all OCT images was also assessed to detect the presence of subclinical cystoid macular edema (CME).

Ocular and systemic adverse events were recorded based on questioning patients or based on observation by investigators.

Statistical Analysis

Sample-size calculations for the primary outcome measures assumed the following: expected anterior chamber flare at 3 days in Group 1 (evaluated by a laser flare meter) of 23.9 ph/msec[5]; expected flare reduction in bromfenac recipients of 30%[17]; a common flare standard deviation (SD) of 9.4 ph/msec[5]; t test for independent group comparison for homoscedastic data, $\alpha = 5\%$; statistical power, 80%. Based on these assumptions, a sample size of 56 patients (28 per group) was calculated (nQuery Advisor, release 7.0, sheet MTT0). Based on a 10% dropout rate, a final sample size of 62 patients (31 per arm) was planned.

The 2-tailed t test for independent group comparison was used to evaluate primary and secondary outcomes. Homoscedasticity was assessed by the Levene test and in case of statistical significance, Satterthwaite adjustments were adopted. For OCGA questionnaire data, each symptom was assessed separately. Results were expressed as the mean values ± SD.

RESULTS

Patient Characteristics

One thousand five hundred eighty-two patients were screened for eligibility during routine preoperative evaluation in the cataract clinic. All individuals with cataract and PXF meeting the inclusion and exclusion criteria were invited to participate. Seven patients did not agree to be included in the clinical trial. Sixty-two patients were randomized for surgery. Among them, 4 were excluded from the study as expected by the protocol (before starting treatment with the study drugs). One patient had active inflammation in the anterior chamber the day of the planned surgery and was not operated on, 2 patients had a posterior capsule rupture with vitreous loss during surgery, and 1 patient developed anterior uveitis with keratic precipitates the day after surgery. The remaining 58 eyes (29 per study group) were treated as per protocol. Patients had advanced cataracts, mostly nuclear sclerosis type N3 (34 [55%]) or N2 (20 [36%]). Baseline characteristics did not differ significantly between treatment groups (Table 1).

Efficacy

Ocular Inflammation Figure 1 shows the amount of inflammation in the anterior chamber over time. Postoperatively, flare was 31% lower in Group 2 than in Group 1 at 3 days (mean 11.92 ± 8.14 ph/msec versus 17.13 ± 9.03 ph/msec) ($P = .025$). The between-group difference was greater 7 days postoperatively, with the mean flare 43% lower in Group 2 (10.77 ± 6.17 ph/msec versus 18.72 ± 12.37 ph/msec) ($P = .003$). Treatment was discontinued at 14 days in both groups as

Table 1. Patient characteristics at baseline.

Parameter	Group 1 (n = 31)	Group 2 (n = 31)
Age (y)		
Mean	77	77
Range	64, 92	60, 89
Females (n)	17	20
Mean CDVA (logMAR)	0.43	0.46
Mean IOP (mm Hg)	15.9	16.5
Mean laser flare (ph/msec)	9.76	9.79
Mean length of surgery (min)	15.9	15.2

CDVA = corrected distance visual acuity; IOP = intraocular pressure

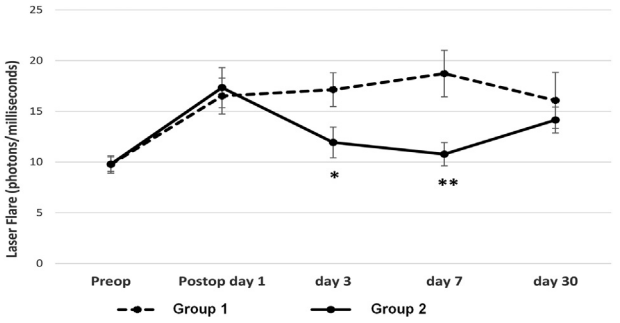

Figure 1. Anterior chamber inflammation measured by laser flare meter in patients with PXF syndrome having cataract surgery. Bars represent standard error (* = P = .025; ** = P = .003).

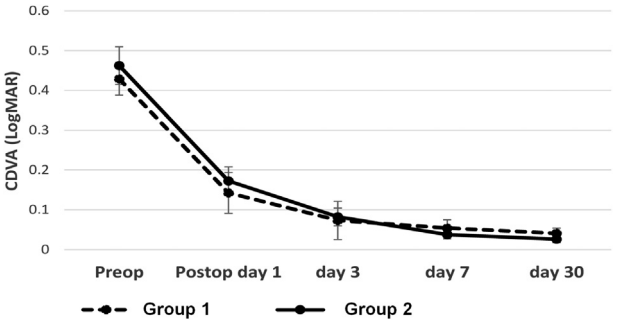

Figure 2. Visual acuity of patients with pseudoexfoliation syndrome having cataract surgery. Bars represent standard error (CDVA = corrected distance visual acuity).

per protocol. At 4 weeks, the flare in Group 1 reached the levels in Group 2 and there was no significant difference between the groups (mean 14.14 ± 6.87 ph/msec versus 16.07 ± 14.91 ph/msec) (P = .529). Steroid alone did not have a noticeable effect on inflammation over time (P < .05 versus baseline at all postoperative assessments).

Secondary Outcomes Visual acuity improved steadily after surgery in both groups at all timepoints (Figure 2). Postoperatively, the mean CDVA was better than 20/30 at 1 day and better than 20/25 by 3 days. The number of patients with 20/20 CDVA 1 week postoperatively was 16 (55%) and 15 (52%) in Group 1 and Group 2, respectively.

The proportion of patients who had ocular pain at 3 days was the same in both arms (1 patient in each group). In general, few patients reported postoperative ocular discomfort. There were no significant between-group differences in the 7 symptoms measured by the OCGA questionnaire (eye pain, tearing, itching, foreign-body sensation, photophobia, eye discharge, and haziness) (data not shown).

Macular Thickness The proportion of patients with macular thickness greater than 300 µm at 4 weeks, the selected secondary endpoint, did not differ significantly between treatment groups but was in favor of bromfenac (3 patients in Group 1 and 1 in Group 2) (P = .07).

Although not a planned study endpoint, an increase in mean macular thickness 1 month after cataract surgery was seen in Group 1 but not in Group 2, resulting in a significant difference between groups at 4 weeks (mean 261.10 ± 34.50 µm versus 243.38 ± 28.23 µm) (P = .03) (Figure 3).

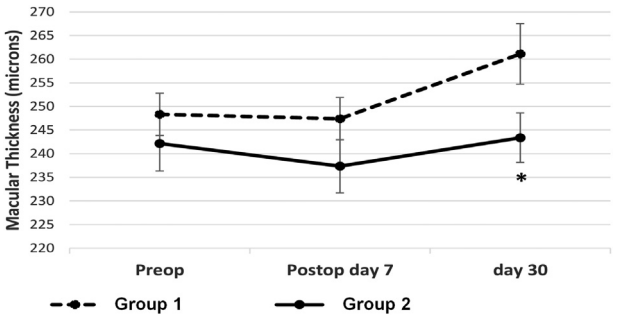

Figure 3. Central macular thickness measured by OCT. Bars represent standard error (* = P = .03).

Subclinical Cystoid Macular Edema No eye in Group 2 had intraretinal cysts on the OCT scans at any time. Four patients on Group 1 had intraretinal cysts at 4 weeks (0% versus 14%) (P < .05) (Figure 4).

DISCUSSION

The results in this trial showed that bromfenac ophthalmic solution significantly reduced inflammation after cataract surgery when added to dexamethasone and tobramycin eyedrops in PXF cases. Patients with PXF have a compromised BAB and therefore develop higher levels of ocular inflammation after cataract surgery.[5,6] Although many clinical trials have assessed the effects of topical NSAIDs on ocular inflammation after cataract surgery, data for patients with PXF are lacking. The combination of topical NSAIDs and steroids seems to be effective in PXF, possibly because of the ability of NSAIDs to restore the BAB more rapidly.

This study found new information regarding postoperative inflammation after phacoemulsification in PXF. Evaluation of operated eyes using the laser flare meter showed subtle aspects of ocular inflammation that could not be detected at the slitlamp. Inflammation in Group 1 did not decrease significantly over time, suggesting that the antiinflammatory effect of dexamethasone alone is less than expected and that topical steroids may be insufficient to control inflammation after cataract surgery in patients with PXF. Moreover, the degree of inflammation in Group 2 increased to a level similar to

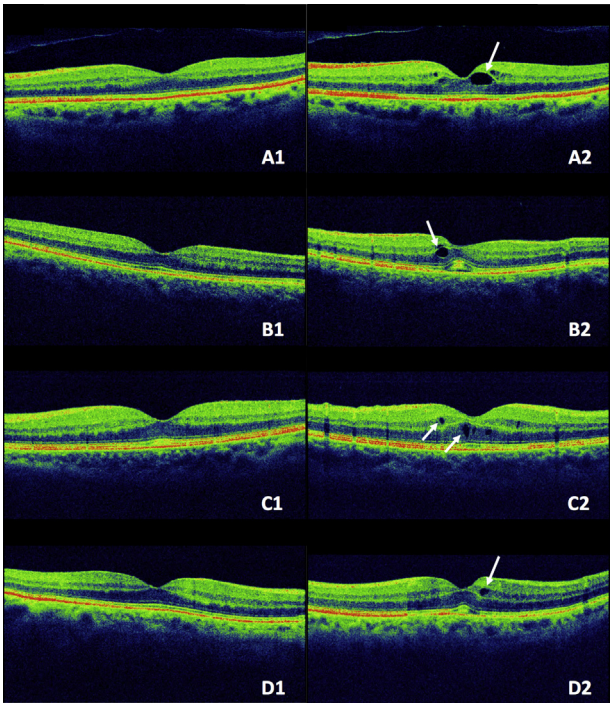

Figure 4. Optical coherence tomography scans of the macular area before (*A1*, *B1*, *C1*, *D1*) and 1 month after (*A2*, *B2*, *C2*, *D2*) cataract surgery in 4 patients who developed subclinical macular edema. Arrows indicate intraretinal cystic spaces on the OCT images 30 days postoperatively.

that in Group 1 when bromfenac was discontinued at 14 days. Bromfenac 0.09% is approved only for the treatment of ocular inflammation in the first 14 postoperative days; however, it seems that longer therapy would have benefited our PXF patients. Finally, in both arms, postoperative flare did not return to preoperative levels by the end of the study (1 month). Eyes with PXF might have prolonged subclinical inflammation after cataract surgery as a result of increased vascular permeability. This long-lasting inflammation might explain the occurrence of pseudophakic macular edema several weeks after uneventful cataract surgery in eyes that appear otherwise unremarkable on slitlamp examination.[9]

Use of laser flare photometry in this study made it possible to accurately measure anterior chamber inflammation. This method is objective and highly reproducible.[24] Most published studies of topical NSAIDs after cataract surgery were based on subjective slitlamp evaluation of postoperative inflammation by an ophthalmologist.[13,14,16] These grading systems were based on uveitis studies and might be inappropriate to use to evaluate clinical conditions in which the amount of postoperative inflammation is minimal, such as after uneventful phacoemulsification.[23] The Standardization of Uveitis Nomenclature Working Group[22] measured anterior chamber flare using a grading scale based on visibility of the iris details using slitlamp examination. The updated laser flare meter FM-700 can precisely differentiate anterior chamber flare on a scale from 2 to 1000 ph/msec.

Pseudophakic macular edema results from the breakdown of the blood–retinal barrier.[10,19] Eyes with PXF are at a higher risk for the development of pseudophakic macular edema.[1] The incidence and the effects on vision of subclinical macular edema after phacoemulsification are probably underestimated.[9] The rates and mechanisms of the progression of subclinical macular edema to a symptomatic form are unknown.[19] The current study showed increased macular thickness 4 weeks postoperatively in patients not treated with bromfenac. Although the study was not designed to adequately estimate macular edema, the difference in central macular thickness on OCT between the 2 groups was statistically significant. This difference could be clinically relevant because changes in macular thickness as low as 10 μm might have a considerable effect on contrast sensitivity.[26]

Intraretinal cysts on OCT were not detected in any bromfenac recipients; however, 4 patients receiving standard care developed subclinical CME at 4 weeks. All cases of intraretinal cysts resolved with appropriate treatment. It is unclear how many patients might have developed a more severe form of macular edema if subclinical findings had not been detected and had gone untreated.

A debate on the role of topical NSAIDs after cataract surgery is ongoing. A recent metaanalysis[11] concluded that NSAIDs are more effective than topical steroids in preventing CME. Unfortunately, this review paper included 6 articles only. Among them, 4 compared topical NSAIDs with fluorometholone 0.1% and not with stronger topical steroids (ie, prednisolone acetate 1.0%). A report by the American Academy of Ophthalmology[27] drew the opposite conclusions. This paper affirmed that there is a lack of level I evidence that supports the long-term benefit of NSAID therapy to prevent vision loss from macular edema after cataract surgery. A successive metaanalysis[28] studied the odds in 17 trials of developing CME within 3 months after phacoemulsification. The combination of NSAIDs and corticosteroids was found to be better than topical steroids alone in reducing the odds of developing CME in nondiabetic patients and in diabetic patients. In addition, NSAIDs given alone significantly reduced the odds of developing CME compared with topical steroids in nondiabetic patients. A retrospective study of 16 070 cataract surgeries[29] compared topical prednisolone alone or in association with a topical NSAID to prevent postoperative macular edema. Adding an NSAID to topical prednisolone significantly decreased the risk for the development of severe macular edema with a visual acuity of 20/40 or worse.

Most published studies of the outcomes after cataract surgery did not present precise methods to measure inflammation, such as laser flare photometry. The lack of standardized reporting of CME based on OCT might limit the estimation of its incidence and the assessment of treatment outcomes. Our study analyzed the effect of steroids and NSAIDs in a specific population (ie, patients with PXF) and found that the combination of the 2 provided better antiinflammatory effects than topical steroids alone. The laser flare meter and high-resolution OCT should be used in larger populations to study the effects of topical steroids and NSAIDs, alone or in combination, on intraocular inflammation after cataract surgery.

WHAT WAS KNOWN

- Postoperative inflammation is higher in patients with PXF syndrome than in patients who have routine cataracts.

WHAT THIS PAPER ADDS

- After cataract surgery, the addition of bromfenac ophthalmic solution 0.09% reduced flare by 31% at 3 days and by 43% at 7 days compared with dexamethasone 0.1% and tobramycin 0.3% ophthalmic solution alone.
- The evaluation of postoperative inflammation with laser flare photometry showed interesting and unexpected aspects in PXF eyes.
- Topical bromfenac and steroid use after cataract surgery provided better antiinflammatory effects than a steroid alone in eyes with PXF.

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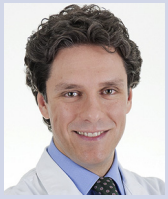

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